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(54) Title: SYSTEMS AND METHODS FOR HIGH PERFORMANCE SCANNING

(57) Abstract

The present invention provides a scanning confocal microscope image detection system having a simple and inexpensive objective lens and a high acceleration/high speed voice coil driven translation system. The objective lens provides high light collection efficiency at low cost. The voice coil provides improved acceleration for fast scanning of at least one axis (scanning direction; fast scan axis) of a polymer array that can be used effectively with the inexpensive objective lens having high light collection efficiency. In one embodiment the translation stage includes a voice coil, a linear slide, and a light weight bracket connecting the voice coil to the linear slide. The bracket is rigid and designed to support a polymer array to be scanned or a turning prism and objective lens. Thus, the present invention provides systems and methods for high speed low cost scanning of, for example, polymer arrays, i.e., high performance cost effective polymer array scanning using a voice coil driven translation stage.

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SYSTEMS AND METHODS FOR HIGH PERFORMANCE SCANNING

The present application relates to provisional U.S. Patent Application Serial No. 60/106,397, filed October 30, 1998, the complete disclosure of which is hereby incorporated herein by reference for all purposes.

GOVERNMENT RIGHTS NOTICE

Portions of the material in this specification arose as a result of Government support under contract number 70NANBG5H1031 between Affymetrix and the U.S. Department of Commerce. The Government has certain rights in this invention.

BACKGROUND OF THE INVENTION

Technical Field of the Invention

The present invention generally relates to the fields of imaging and scanning. In particular, the present invention provides scanning systems and methods for high speed scanning and imaging of a sample containing labeled materials, for example scanning arrays of polymer sequences such as oligonucleotide arrays.

Description of the Related Art

Polymer arrays, for example, DNA arrays, are known as shown

in patent application U.S.S.N. 08/811,829 ('829) and U.S. Patent Nos. 5,744,305; 5,445,936; and 5,677,195; which are hereby incorporated by reference in their entirety for all purposes. The polymer arrays, such as the GeneChip® probe array (Affymetrix, Inc., Santa Clara, CA), can be synthesized using light-directed methods described, for example, in U.S. Patent Nos. 5,143,854; 5,424,186; 5,510,270; and PCT published application no. WO 95/11995, which are hereby incorporated by reference in their entirety for all purposes. In one method, an array containing synthesized single stranded nucleic acids such as DNA, is enclosed in a protective package, as shown in patent applications U.S.S.Nos. 08/528,173 and 08/485,452 which are hereby incorporated by reference in their entireties for all purposes. The array is contacted with a sample containing single stranded DNA that is labeled using for example fluorescent labels such as fluorescein or phycoerythrin, and which hybridizes to the single stranded DNA on the array. After hybridization, the array (either packaged or not packaged) is placed into a device generally known as a scanner that obtains a fluorescence image of the array in order to analyze hybridization between the single stranded nucleic acids on the array and in the sample.

Systems (scanners) and methods for detecting marked targets on polymer arrays are generally known. Typically the polymer array is scanned using a scanner that directs a point of light in a rectilinear raster fashion so as to image the entire polymer array. A scanner may include a confocal

microscope with a light source for generating light directed to the polymer array, a photodetection mechanism for detecting light emitted from the polymer array, and a computer controlled translation table that moves the polymer array in three (XYZ) directions. One direction is the fast scan direction (e.g., X direction), another is the slow scan direction (e.g., Y direction) and the third direction is a focus direction (e.g., Z direction).

As an example, the scanner projects a point of light onto a surface of the polymer array and is focused by the translation stage in the focus direction; Z direction. Next, the translation stage rectilinearly fast scans the point of light from one side of the polymer array to another by moving the polymer array in for example the X direction, so as to scan one line of the polymer array, point by point. During the fast scan the photodetection mechanism detects the light emitted from the surface of the polymer array so as to obtain a fluorescence image of the polymer array. Once one line in the fast scan (X) direction has been scanned the translation table moves the polymer array incrementally approximately the thickness of one scan line in the slow scan (Y) direction. This raster scanning continues until the entire surface area of the polymer array has been scanned. (See for example U.S. Patent No. 5,631,734 issued to Stern et al., which is hereby incorporated by reference in its entirety for all purposes.)

There is a need for a polymer array scanner which is reasonable in cost and provides high polymer array scanning throughput and high resolution, e.g.

1.5 μm , 3.5 μm, or smaller pixel size over a 14 mm x 14 mm field.

SUMMARY OF THE INVENTION

The present invention provides systems and methods for image scanning of, for example, polymer arrays. The invention provides means for moving a linear translation stage of a scanning system with a speed of at least 10 scanning lines/second, preferably at least 20 scanning lines/second and more preferably at least 30 scanning lines/second over a scanning distance of at least 2 mm, preferably at least 5 mm, and more preferably at least 14 mm. The scanning system is capable of scanning with pixels having a size of approximately 3.5 μm or less, preferably having a size of approximately 2 μm or less, and more preferably having a size of approximately 1.5 μm or less, while maintaining the fast scanning speeds indicated above and accurately detecting an image. In some embodiments, the scanner includes a voice coil to provide scanning motion for at least one of the X direction, Y direction, and Z direction translation of a polymer array analysis system. The acceleration of the voice-coil-driven axis of the present invention is high (e.g., 13.7 G, where G is the acceleration due to gravity) and can not easily be achieved with stepping motors. The high acceleration, combined with the high steady-state scan speed of the voice-coil-driven axis (about 22 inches/second), enables the voice coil scanner of the present invention to scan a distance of, for example, 14 mm (length of scan line of one type of polymer array) at 30 lines/second.

The voice coil scanner of the present invention can use either stationary optics or a moving scan head. In either case, the voice-coil-driven axis is the X axis. In one embodiment, the voice coil drives a lightweight linear slide mounted on a 2-axis (YZ) translation table. This linear slide serves as the support for a polymer array (scanned sample). In another embodiment, the voice coil drives a scan head, i.e. a lightweight linear slide that supports a turning prism or turning mirror and an objective lens, while the polymer array is supported by the 2-axis (YZ) translation table. Further, a motion control system is provided to monitor and control the motion of the voice coil for fast accurate scanning of the polymer array.

Using a voice coil for high speed scanning of polymer arrays in the fast axis (X) direction, rather than using a galvanometer driven scanning mirror, enables the use of a simple low cost objective lens having a high numerical aperture (for example, 0.5 or greater). The objective lens can be, for example, a microscope objective lens or a single element aspheric lens. This objective lens can have high numerical aperture while being small and inexpensive because it does not have to be corrected for off-axis aberrations, unlike the objective lens in a galvo scanner. All other things being equal (laser power, spot size, etc.), a scanner with an objective numerical aperture of 0.5 operating at 30 lines/second produces images with the same signal-to-noise ratio as a scanner with an objective numerical aperture of 0.25 operating at 7.5 lines/second.

As a result of using the combination of a voice coil driven translation stage and a simple high efficiency objective lens, the voice coil scanner of the present invention can achieve fast scanning and high polymer array throughput. For example, the voice coil scanning system of the present invention, with an objective lens having a numerical aperture of 0.5 or greater, can achieve accurate and reliable polymer array scanning at a speed of at least 10 lines/second, preferably at least 20 lines/second and more preferably at least 30 lines/second.

Therefore, the present invention provides a scanning system with a simple and inexpensive objective lens and a high acceleration / high speed voice coil driven translation stage that can rapidly scan, for example, 12.8 mm x 12.8 mm polymer arrays using a pixel size of, for example, about 3.5 μm or smaller, more preferably 2 μm or smaller and most preferably 1.5 μm or smaller. The voice coil provides improved acceleration for fast scanning of at least one axis of a polymer array. As a result, the present invention provides systems and methods for accurate, high speed, low cost scanning of polymer arrays, i.e., high performance cost effective polymer array scanning.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a top view of one embodiment of a voice-coil-driven translation stage for the scanning system according to the present invention.

Fig. 2 is an end view of one embodiment of a voice-coil-driven

translation stage with an encoder readhead for the scanning system according to the present invention.

Fig. 3 is a top view of another embodiment of a voice-coil-driven translation stage for the scanning system according to the present invention.

Fig. 4 is an end view of another embodiment of a voice-coil-driven translation stage and an encoder readhead for the scanning system according to the present invention.

Fig. 5 is an illustration of a scanning system according to the present invention having a 3-axis XYZ translation system with one fast axis (X axis) driven by a voice-coil.

Fig. 6 is an illustration of a scanning system according to the present invention having a turning prism and objective lens mounted on a single axis voice-coil driven translation stage.

Fig. 7 is a block diagram of one embodiment of a motion control system according to the present invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

Scanners may be characterized in one or more of a number of categories. A point-scanning confocal microscope with stationary optics focuses a beam of light to a stationary point and obtains a 2-dimensional image by moving the sample (e.g., a polymer array substrate) in 2 dimensions, for example X and Y directions (there may also be a 3rd dimension, the Z

direction, for focusing). As described above in the Background section, it scans a single point of light from one side of a sample to another side in one direction, e.g., X direction, (i.e., scanning one line) then moves the sample incrementally in another direction, e.g., Y direction, until all points of the sample are scanned.

One early example of such a scanner with limited application was developed by Marvin Minsky in 1955. (See the "Memoir on inventing the confocal scanning microscope," Scanning 10, 128-138 (1988), at web site http://www.ai.mit.edu/people/minsky/papers/confocal.microscope.txt.) Minsky uses a simple magnetic solenoid without computer control to move a flexure translation stage. H.T.M. Van der Voort et al. describe a similar but more modern system in Scanning 7, 66-78 (1985). The details for their scanning system is provided in the article H.J.B. Marsman et al., "Mechanical scan system for biological applications," Rev Sci Instrum 54, 1047-1052 (1983). Like Minsky, this point scanner uses flexure stages. Flexure translation stages are well suited for scanning small distances, for example 1 mm, but not for the larger distances, for example 14 mm, required for scanning polymer arrays.

One point-scanning confocal microscope with stationary optics useful for point scanning polymer arrays was disclosed by the present inventor in U.S. Patent No. 5,631,734, which is hereby incorporated by reference in its entirety for all purposes. Since this system needs to scan polymer arrays it is

provided with a large scan length sufficient to scan one dimension of a polymer array (e.g., scan length is 14 mm when array size is 12.8 mm x 12.8 mm) and thus uses a crossed roller bearing XYZ translation table, for example a JMAR Precision Systems (Chatsworth, CA) "Slimline" or "Microline" table, instead of a flexure stage. This XYZ translation table is stepper motor driven and moves the polymer array relative to the fixed microscope objective lens to scan the polymer array along one scan line at a time. Either a lead screw or a ball screw converts the rotary motion of the stepper motor to linear motion. Scan speed with this system is limited because of the limited acceleration possible with stepping-motor-driven translation stages.

Another type of confocal microscope scanner is illustrated by a Molecular Dynamics (Sunnyvale, CA) scanner as shown in U.S. Patent No. 5,459,325. This can be called a "point-scanning confocal microscope with a moving scan head." The scan head consists of a turning mirror (or turning prism) and objective lens mounted on a single-axis translation stage. As the scan head moves in this confocal microscope scanner, the focused laser beam moves along with it. The sample is mounted on a separate translation table that moves perpendicular to the scan head. The system obtains a 2-dimensional image by oscillating the scan head rapidly in one dimension and moving the sample slowly in another. The scan head is made small and light so that it can move fast. However, if the scan head is actuated with a stepper motor it suffers from a similar limitation in scanning speed as the point-

scanning confocal microscope with stationary optics due to the stepper motor's slow acceleration.

In all of the confocal microscopes described above, the laser beam is always coaxial with the optical axis of the objective lens, and so is the reflected or emitted light (e.g., fluorescent light) that is collected by the objective lens. The objective lens can be relatively simple and inexpensive because it doesn't have to be corrected for off-axis aberrations. A narrow-angle lens, i.e. a lens that only has to focus light onto or nearly onto its optical axis, is easier to design and manufacture and contains fewer optical elements than a wide-angle lens having the same focal length, f number, resolution, etc. For example, an inexpensive 1 or 2-element lens system may be capable of focusing a laser beam to a 3-micron-diameter spot when the laser beam is coaxial with the optical axis of the lens. If the laser beam enters the lens several degrees off axis and consequently focuses several millimeters off axis, it will probably focus to a much larger spot size. If a 3-micron-diameter spot several millimeters off axis is needed, a more complicated and expensive lens will be required.

Another scanner used for polymer array analysis is a galvanometer-scanning confocal microscope ("galvo scanner") as disclosed in patent application U.S.S.N. 08/856,642 ('642), which is hereby incorporated herein by reference in its entirety for all purposes. The galvo (galvanometer) scanner includes a radial direction system with a galvanometer actuating a mirror to

rapidly scan a laser light spot across a substrate (e.g., a polymer array). The galvo scanner is much faster than the scanners described above, achieving scanning speed of approximately 30 lines/second, but requires a large and expensive objective lens.

In operation, the galvo scanner ('642) uses an angularly oscillating mirror (a mirror mounted on a galvanometer) to direct the laser beam into an objective lens. The lens focuses the laser beam to a spot that moves back and forth over a distance of 14 mm as the mirror oscillates. The objective lens must therefore be corrected for aberrations up to 7 mm off axis. The same lens is used to collect fluorescence from the sample polymer array. The sample is mounted on a translation table and the scanner obtains a 2-dimensional image by moving the focused laser spot rapidly back and forth in one dimension and stepping the sample slowly in another. Thus, the galvo scanner is potentially very fast because galvanometers can oscillate at tens or hundreds of cycles per second. However, the objective lens is large and expensive because must be corrected for off-axis aberrations.

The objective lens in the '642 galvo scanner, for example, is 4 inches long and 2.5 inches in diameter and contains 6 optical elements. This objective lens has a numerical aperture of only 0.25, which means that it collects only about 1 out of 100 photons emitted by the sample. A higher numerical aperture is desirable. Higher numerical aperture results in higher collection efficiency and therefore better signal-to-noise ratio, all other things

(laser power, scan speed, etc.) being equal. Unfortunately, a lens with the same resolution as the current lens (about 3 microns), but a significantly higher numerical aperture (e.g. 0.5) either would have a much smaller field of view (in which case a 12.8 mm x 12.8 mm polymer array would have to be scanned in 2 or more sections) or would be even more complicated and expensive.

Another galvanometer-scanning confocal microscope is provided by Hewlett-Packard as disclosed in U.S. Patent No. 5,585,639. It is a galvanometer-scanning confocal microscope but contains three multi-element lenses: one lens focuses the laser beam onto the sample, and a pair of lenses collects the fluorescence. Thus, this scanner is also expensive to build.

Another type of scanner is the "line scanner" which is different from all of the "point scanners" discussed above. Line scanners image an entire scan line at one time. For example, a "line scanner" is disclosed in U.S. Patent Nos. 5,578,832 and 5,834,758, which are hereby incorporated herein by reference for all purposes. This scanner focuses the laser beam not to a point, but to a line a few microns wide and, for example, 14 mm long, so as to image one entire line of the polymer array sample at a time. An objective lens (or a pair of objectives back to back) collects fluorescence and images the fluorescence onto a linear CCD having 1024 or more pixels. The polymer array sample is mounted on a translation table. Thus, the line scanner obtains a 1-dimensional image with no motion and a 2-dimensional image with only

one axis of motion. Therefore, the line scanner can potentially be very fast because there is no need for a fast scan axis - scan speed is limited not by mechanical considerations such as the acceleration of a stepping motor connected to a translation table or scan head, but by the speed of the electronics or software. However, a linear-CCD-based scanner is optically complicated.

The present invention provides systems and methods for achieving high speed cost effective scanning and imaging of a sample containing labeled materials, for example scanning arrays of polymer sequences such as oligonucleotide arrays. The invention has a wide range of uses, particularly those requiring quantitative study of a microscopic region from within a larger region. For example, the invention can obtain a fluorescence image of a 14 mm x 14 mm area with 1.5 μm or 3.5 μm , or smaller pixels. For example, the invention may find application in the field of histology (for studying histochemical stained and immunological fluorescent stained images), or fluorescence in situ hybridization. In one application, the invention herein is used to image a packaged polymer array, for example a GeneChip® probe array.

In general, the invention provides a scanning system capable of scanning an image with pixels having a size of approximately 3.5 μm or less with a means for moving a linear translation stage that can attain a speed of at least 10 scanning lines/second, and preferably at least 30 scanning

lines/second, while accurately detecting the image. Such a system may include, for example, a voice coil that provides increased acceleration and resulting fast scanning speed.

A scanner employing a voice coil driven translation stage may combine the speed of a galvo scanner with the optical simplicity of a point-scanning confocal microscope with stationary optics (e.g., the scanner disclosed in USPN 5,631,734 hereby incorporated by reference herein) to obtain accurate and reliable image detection using, for example, a 1.5 or 3.5 μm or smaller pixel size. Voice coil actuators are direct drive, limited motion devices that utilize a permanent magnet field and a coil winding (conductor) to produce a force proportional to the current applied to the coil.

One example of an appropriate voice coil is linear actuator voice coil Model No. LA14-24-000 offered by Kimco Magnetics Division of BEI Technologies Inc. Another example of an appropriate voice coil is linear actuator voice coil Model No. LA34-37-000A also offered by Kimco Magnetics Division of BEI Technologies Inc. (See "Voice coil actuators: An applications guide" provided by Kimco Magnetics Division, BEI Technologies Inc, San Marcos CA.) These are two examples of voice coils that are useful in the present invention for driving a translation stage. These are merely examples of voice coils readily available that can work in the present invention. Many other voice coils could work as well. For example, a voice coil for driving a translation stage in the present invention could be custom

designed (i.e., by BEI Kimco or another company) if necessary.

The use of the readily available standard voice coils for driving a translation table could cause the voice coil to overheat and fail if it is required to move too much weight. For example, if a voice-coil-driven stage scans 14 mm at a speed of 560 mm/sec, then the time to scan 14 mm is 25 msec. If we allow 4.166 msec for acceleration and another 4.166 msec for deceleration, then the acceleration or deceleration is 134.4 m/sec^2 (13.7 g, where g is the acceleration due to gravity) and the total time to scan one line is 33.333 msec. If the moving parts weigh 0.5 lb, then the force required for 13.7 g of acceleration is 6.85 lb. The BEI Kimco LA14-24-000 voice coil, for example, has a force constant of 1.6 lb/amp. The current required for 6.85 lb of force is therefore 4.28 A. The coil has a resistance of 7 ohms when hot. The power dissipated in the coil at 4.28 A is therefore 128 W. When the stage is not accelerating or decelerating, the current is zero, which means that the average power dissipated in the coil is 32 W. The coil has a thermal resistance of 3.4°C/W, which means that the coil temperature is 134°C if the ambient temperature is 25°C. The coil is rated for a maximum temperature of 130°C.

The previous example calculations ignore friction and do not include a safety margin. However, it is conservative in that there is probably no need for the moving parts to weigh 0.5 lb if the system is properly constructed.

The scanning system should be constructed so as to take advantage of the fast acceleration of the voice coil while ensuring that the weight the voice

coil must move is less than the weight which will cause the voice coil to overheat and fail due to excessive power dissipation. The moving part of, for example, an NB Corporation of America (Wood Dale, IL) model SER9A slide weighs approximately 20 grams (see illustration in Fig. 2, item 10 and Fig. 4 item 25). A variety of linear slides, using either linear or recirculating ball bearings, linear or recirculating crossed roller bearings, or air bearings, may be suitable. A packaged DNA array weighs, for example, 16 grams. The moving part of the LA14-24-000 voice coil weighs approximately 22 grams. If the bracketry that holds all of these moving parts together is designed to weigh, for example, 55 grams, and the scanner is designed so that these are the primary components that the voice coil must move, then the total weight of the moving parts is approximately 0.25 lb, and the power dissipated in the coil is only 25% of what was calculated above (actually less than 25% of what was calculated above, because the voice coil resistance is only 5 ohms when operating cool). Furthermore, the voice coil can be cooled with forced air (e.g. a fan, or a jet of compressed air) if additional cooling is needed to improve performance.

The LA14-24-000 can provide improved scanning time over conventional scanners that use stepper motors to drive the fast scan axis, i.e., a decrease in the amount of time it takes to scan each line of the fast scan axis when scanning a polymer array. The steady-state scan speed of a scanner using the LA14-24-000 in inches/second is about 22 inches/second and the

acceleration is very high, about 13.7 G (where G is the acceleration due to gravity), enabling the device to scan 14 mm at 30 lines/second. This speed is comparable to the maximum scan speed of the galvo scanner. However, in practice the galvo scanner, having a low numerical aperture objective lens, may be operated at considerably less than this maximum speed because of lower signal-to-noise ratio at the higher speeds.

The voice coil scanner can be designed so that a voice-coil-driven translation stage operates to move either the polymer array (i.e., similar to the point-scanning confocal microscope with stationary optics previously discussed) or the objective lens and turning mirror (similar to the Molecular Dynamics scanner previously discussed) in the fast axis (X) direction. The slow axis (Y direction) and the focus axis (Z direction) can be driven by stepping motors, although voice coils also can be used for these axes.

Referring now to Figures 1 and 2, a first preferred embodiment of the invention having a voice coil driven translation stage mechanized to move the polymer array in the fast X axis direction is illustrated. This embodiment uses a slide type voice coil. The voice coil scanner of this embodiment has a voice coil translation stage 15 which includes a voice coil magnet and mounting bracket 1 mounted in a stationary manner to the top surface 13 of a 2-axis (YZ) translation table. The voice coil has a moving coil 2 that moves along a slide in the fast axis (X axis) direction in response to current provided to wires 3. The voice coil used in this embodiment may be, for example, a BEI Kimco

Magnetics Division Voice Coil Linear Actuation Model No. LA14-24-000 or any other voice coil having similar or better thermal, mechanical, and electrical characteristics. All else being equal, the weight of the moving coil should be minimized, the force constant of the coil (in pounds per amp) should be as large as possible, and the thermal resistance of the coil (in degrees per watt) should be as small as possible.

The moving coil 2 of the voice coil is connected to the movable part 10 of a linear slide by bracket 4. This bracket should be made of a design and material so that it is light weight so as to require minimal translation force and strong enough to remain rigid during oscillation of the linear slide. For example, the bracket may be made of steel or aluminum and have a weight of up to 55 grams. Although bracket 4 is illustrated as one piece it may be made of multiple pieces. Bracket 4 has a surface 5 upon which an encoder scale 8 is mounted. The encoder scale 8 operates with the encoder readhead 11 to monitor the position of a polymer array sample 9 mounted to the sample mounting surface 6 of bracket 4. The weight of the encoder scale should also be minimized as much as possible since it is connected to the moving parts of the voice coil translation stage. The readhead 11 is mounted to the top surface 13 of the 2-axis translation stage by readhead mounting bracket 12. The readhead 11 and the scale 8 may be, for example, a Renishaw Inc. (Schaumburg, IL) RGH22Z readhead and a Renishaw RGS-S scale, respectively.

The stationary guide portion 7 of the linear slide is mounted to the top surface 13 of the 2-axis translation table. The linear slide should be selected so that the weight of the moving part 10 and friction coefficient of the linear slide is minimized so that the force require by the voice coil and thereby the power dissipation of the voice coil are within the thermal capability of the voice coil. The linear slide may be, for example, NB Corporation of America crossed roller bearing linear slide, model SER9A, or any other ball bearing, crossed roller bearing, or air bearing linear slide that meets the mechanical and operational qualities for reliable fast axis translation of the polymer array.

The 2-axis translation table having top surface 13 may be, for example, a JMAR Precision System 2-axis Slimline or Microline translation table or any other translation table that can provide reliable 2-axis translation. As illustrated in Fig. 2, the translation table will provide movement in the slow axis (Y axis) direction and the focus axis (Z axis) direction. If a 3-axis translation table with sufficiently long travel is used, the present invention has the capability of scanning an entire wafer of polymer arrays sequentially, one array at a time.

In operation the voice coil translation stage 15 is provided a driving current from an amplifier (e.g., a servoamplifier) through wires 3. The moving part 2 of the voice coil moves the bracket 4, encoder scale 8, polymer array 9, and moving part 10 of the linear slide in the fast axis x direction along the guide part 7 of the linear slide. A control system senses the location of the

polymer array 9 using information from the encoder readhead 11 and indicates when one complete translation in the x direction is complete. Once one complete x direction fast axis scan is complete the translation table will index approximately the width of one fast scan line in the slow axis Y direction and the controller will trigger another fast scan by the voice coil. This sequence occurs repeatedly until the entire polymer array, or a predefined portion thereof, has been scanned by a confocal microscope image system.

If a 3-axis translation table is being used to scan a wafer of polymer arrays, the x direction axis of the 3-axis translation table will then move to the next polymer array on the wafer and the above described polymer array scanning sequence will be repeated. Once all arrays in a row on the wafer have been scanned the translation table will move in the slow axis Y direction to the next row of arrays to be scanned. These steps will be repeated until the entire wafer of polymer arrays has been scanned.

Figures 3 and 4 illustrates another preferred embodiment of the invention having a voice coil driven translation stage mechanized to move a scanning beam of light across a polymer array in the fast X axis direction. This embodiment uses a plunger type voice coil, for example, a BEI Kimco model LA34-37-000A or any other voice coil having similar mechanical and electrical characteristics. The voice coil scanner of this embodiment has a voice coil translation stage 30 which includes a voice coil mounting bracket 16, a voice coil magnet and housing 17 (stationary part of the voice coil), an

electrical coil winding section 18 (moving part of the voice coil), and wires 19 connecting to the coil 18.

Unlike the previous embodiment, the voice coil mounting bracket 16 is not mounted to the top surface 13 of the 2-axis translation stage. Rather, the voice coil mounting bracket 16 can be mounted to another structure which is preferably stationary relative to the confocal microscope image system used in the scanning system.

The moving coil 18 of the voice coil is connected to the moveable part 25 of a linear slide by bracket 20. This bracket should be made of a design and material so that it is lightweight so as to require minimal translation force and strong enough to remain rigid during oscillation of the linear slide. For example, the bracket may be made of steel or aluminum and have a weight in the range of up to 0.5 lb. Although bracket 20 is illustrated as one piece it may be made of multiple pieces. Bracket 20, like bracket 4 of the previous embodiment, has a surface upon which an encoder scale 21 is mounted. A turning mirror, penta-prism, or right-angle prism 22 (reflector) and objective lens 23 are mounted on the bracket 20 opposite the encoder scale 21. The encoder scale 21 operates with the encoder readhead 27 to monitor the position of the scan head. To minimize image distortion due to pitch and yaw of the linear slide, encoder scale 21 should be as close as possible to the focal point of lens 23. The encoder scale 21, turning prism 22, and objective lens 23, should be light weight to ensure the voice coil does not overheat. The

readhead 27 and the scale 21 may be, for example, a Renishaw RGH22Z readhead and a Renishaw RGS-S scale. However, another type of position sensing system may be used, for example a Zeiss encoder. The readhead 27 is mounted to the top surface 26 of an optical breadboard, for example a Newport Corp (Irvine, CA) RG series breadboard, by read head mounting bracket 28.

The guide portion 24 of the linear slide is mounted to the top surface 26 of the optical breadboard. The linear slide should be selected so that the weight of the moving part 25 is minimized to minimize the force required by the voice coil and thereby the power dissipation of the voice coil are within the thermal capability of the voice coil. The linear slide may be, for example, Parker/Daedel (Harrison City, PA) crossed roller bearing linear slide model CR4501, or any other ball bearing, crossed roller bearing, or air bearing linear slide with sufficient straightness and flatness of travel and sufficiently light weight that it can operate at the desired speed.

In this embodiment, the moving parts are much heavier (for example, 2 lb) than in the previous embodiment. However, the voice-coil-driven linear stage is still able to scan 14 mm at 30 lines/second without overheating because of the thermal and electrical characteristics of the LA34-37-000A voice coil (the force constant is 5.4 lb/amp, the resistance is 1.4 ohms, and the thermal resistance is 2.2 degrees C per watt).

Unlike the previous embodiment, the guide portion 24 of the linear slide is not directly connected to the top surface 13 of the 2-axis (or 3 axis)

translation table. Rather the 2-axis translation table having top surface 13 has the polymer array sample 9 mounted directly to it and is adjacent to the voice coil driven translation stage. The surface of polymer array 9 is perpendicular to the optical axis of scan head objective lens 23. The 2-axis translation table having top surface 13, may be for example, JMAR Precision System 2-axis Slimline or Microline translation table or any other translation table that can provide reliable 2-axis translation. As illustrated in Fig 4, the translation table will provide movement of the polymer array in the slow axis (Y) direction and the focus axis (Z) direction.

In operation, the voice coil translation stage 30 is provided a driving current from an amplifier (e.g., a servoamplifier) through wires 19. The moving part 18 of the voice coil moves the bracket 20, encoder scale 21, turning mirror or prism 22, objective lens 23, and moving part 25 of the linear slide in the fast axis (X) direction along the guide part 24 of the linear slide. The scan head comprised of the turning mirror or prism 22 and the objective lens 23 mounted on the bracket 20 will scan a point of light from a laser light beam on to the surface of the polymer array 9 in a linear manner in the fast axis (X) direction. A control system senses the location of the scan head using information from the encoder readhead 27 and indicates when one complete translation in the X direction has been completed. Once one complete X direction fast axis scan is complete the translation table will index approximately the width of one fast scan line in the slow axis (Y) direction and

the controller will trigger another fast scan by the voice coil. This sequence occurs repeatedly until the entire polymer array, or a predefined portion thereof, has been scanned.

As with the first embodiment, if a 3-axis translation table is being used to scan a wafer of polymer arrays, the x direction axis of the 3-axis translation table will then move to the next polymer array on the wafer and the above described polymer array scanning sequence will be repeated. Once all arrays in a row on the wafer have been scanned the translation table will move in the slow axis (Y) direction to the next row of arrays to be scanned. These steps will be repeated until the entire wafer of polymer arrays has been scanned.

Figures 5 and 6 illustrate two alternative confocal imaging systems that may be used for the present invention in detecting, for example, florescence emitted by targets bound to the polymer arrays. Alternative confocal imaging systems that may be modified to use a voice coil fast axis translation stage include those found in USPN 5,631,734 and U.S. Application Ser. No. 08/856,642, which are hereby incorporated herein for all purposes. The system of U.S. Application Ser. No. 08/856,642 would be further modified to eliminate the galvo scanning mirror and to have a simple inexpensive objective lens mounted in a stationary position or within a scan head. A brief description of the configuration and operation of the confocal imaging systems shown in Figs. 4 and 5 follows. A more detailed understanding of the overall operation of the confocal imaging systems described herein can be obtained by

reading USPN 5,631,734 and U.S. Application Ser. No. 08/856,642, herein incorporated by reference.

Figure 5 illustrates a confocal imaging system having a stationary (fixed position) objective lens 115. The sample 9 is mounted on a 3-axis translation stage 15 having a voice-coil-driven fast (X) axis.

As illustrated in Fig. 5, the confocal imaging system includes a laser 103 for generating a laser light beam that is transmitted through beamsplitter 104, reflected by dichroic beamsplitter 114, and focused by objective lens 115 onto the surface of polymer array sample 9. The laser light that is reflected by the surface of polymer array sample 9 is collimated by objective lens 115, reflected by dichroic beamsplitter 114 and beamsplitter 104, and focused by lens 102 onto pinhole 101. The portion of the reflected laser light that is transmitted through pinhole 101 is detected by photodiode 100. Photodiode 100 provides a signal to a controller to adjust the position of the sample so that the laser beam is focused on the surface of the polymer array sample 9. The controller will activate, for example, a stepper motor in the 2-axis (YZ) translation table so as to move the translation table in the focus axis (Z) direction until the laser light beam is properly focused on the surface of the polymer array sample 9.

In another embodiment (not shown in a figure), the sample is mounted on a 2-axis (XY) translation stage having a voice-coil-driven fast (X) axis, and the objective lens is mounted on a separate single-axis (Z) translation stage. In

this embodiment the Z translation stage can be very small and light (for example, the "PIFOC" piezoelectric microscope focusing device available from Polytec PI, Inc., Auburn, MA) because only the objective lens is mounted to it.

The confocal imaging system of Fig. 5 also includes two photomultiplier tubes (PMT) 105 and 112, each one for detecting fluorescence having a particular range of wavelengths emitted from the surface of the polymer array sample. For example, PMT 112 may detect fluorescence from fluorescein-labeled target molecules and PMT 105 may detect fluorescence from phycoerythrin-labeled target molecules. The PMT (105, 112) may be, for example, a Hamamatsu R4457 or R6357 photomultiplier tube , or any other PMT having sufficiently high quantum efficiency at the wavelengths of interest and sufficiently low dark current. Various types of light detectors other than a PMT also may be used, including photodiodes, avalanche photodiodes, phototransistors, vacuum photodiodes, and other light detectors.

The confocal imaging system of Fig. 5 further includes optical trains to separate, for example, two unique colors of fluorescent light. A first color fluorescent light is emitted from a particular marked target on the polymer array sample 9 surface, collimated by objective lens 115, transmitted through dichroic beam splitters 113 and 114, lens 110, pinhole 108, and bandpass filter 106, and sensed by PMT 105. Similarly, a second color fluorescent light different from the first color fluorescent light is emitted from a different

particular marked target on the polymer array sample 9 surface, collimated by objective lens 115, transmitted through dichroic beam splitter 114, reflected by dichroic beamsplitter 113, transmitted through lens 111, pinhole 109, and bandpass filter 107, and sensed by PMT 112.

Figure 6 illustrates a confocal imaging system having an objective lens 23 and turning mirror or prism 22 mounted on a voice-coil-driven translation stage 30 that moves in the fast-scan (X) direction. The sample 9 is mounted on a separate 2-axis (YZ) translation stage.

Laser 103 produces a laser light beam that is transmitted through beamsplitter 104, reflected by dichroic beamsplitter 114 and turning mirror or prism 22, and focused by objective lens 23 onto the polymer array sample 9 surface. As the scan head moves back and forth in the X direction, the laser beam and the collected fluorescence remain centered on mirror or prism 22 and objective lens 23. Lens 102, pinhole 101, and photodiode 100 are used for detection of reflected laser light and provide the sensing capability for adjusting the focus of the laser light beam. Lens 110, pinhole 108, bandpass filter 106 (or longpass filter), and PMT 105 enable sensing of, for example, one color fluorescent light emitted by one type of target on the polymer array 9 surface. Thus, this confocal imaging system can only detect, for example, one color fluorescent light emitted from one type of target on the polymer array surface because it does not include dichroic beamsplitter 113, lens 111, pinhole 109, and PMT 112.

In this embodiment, the voice coil translation stage 30 has a turning prism 2 and objective lens 23 securely mounted on a scan head. The laser light beam from laser 103 is reflected by dichroic beamsplitter 114 onto turning prism 22 and through the objective lens coaxial with the objective lens's optical axis. The laser light beam strikes the turning prism 22 surface at the same location and remains coaxial with the optical axis of the objective lens 23 throughout the fast axis (X) translation of the scanning head. As a result, the laser light beam scans a line on the surface of the polymer array in the fast axis (X) direction using the movement of the scan head rather than the movement of the polymer array sample 9.

Many alternative configurations of the confocal imaging systems described above are possible. For example, a system having 2 PMTs as shown in Fig 5 can be used with a moving scan head instead of stationary optics. A system having one PMT as shown in Fig 6 can be used with stationary optics instead of a moving scan head. It is to be understood that the confocal imaging system of the present invention could have any number of lasers, PMTs and related optical trains, as many as the number of different types of light to be uniquely detected. Furthermore, a slide-type voice coil can be used to operate a moving scan head and a plunger-type voice coil can be used with stationary optics, or vice versa.

The objective lens for a voice coil polymer array scanner can be a microscope objective (for example Rolyn Optics, Covina CA, model 80.3090,

0.65 numerical aperture) or a single-element aspheric lens (for example ThorLabs, Newton NJ, model 350330-A, 0.68 numerical aperture). A single-element aspheric lens is significantly smaller and lighter than a microscope objective and thus may be better for the scan head embodiment of the present invention. A single-element aspheric objective lens is not corrected for chromatic aberrations, but if the focal length is small enough, chromatic correction may not be necessary. For example, the ThorLabs 350330-A has a focal length of 3.1 mm, and the axial color at 580 nm (approximately the phycoerythrin emission peak) is only about 0.33 microns per nanometer (i.e. 0.33 micron change in focal length per 1 nm change in wavelength). Alternatively, a custom 2-element cemented doublet (for example, a biconvex BK7 element cemented to a biconcave SF6 element) can be used to correct for the axial color introduced by the single-element aspheric lens. The doublet can be placed either between lens 23 and mirror or prism 22 or between dichroic beamsplitter 114 and mirror or prism 22.

Other types of objective lenses can also be used, for example a refractive/diffractive hybrid lens (i.e. a lens having at least one refractive surface and at least one diffractive surface), or a 2-element aspheric lens having a numerical aperture of 0.85 (Sony patent 5,880,893).

An objective lens with a numerical aperture of 0.68 has about 8 times the collection efficiency of a lens with a numerical aperture of 0.25. As discussed above, although the galvo scanner is capable of scanning at 30

lines/sec, it is often operated at 7.5 lines/sec because the collection efficiency of its objective lens and signal-to-noise ratio at 30 lines/sec is insufficient for some assays. A voice coil scanner running at 30 lines/sec provides a better signal-to-noise ratio than a galvo scanner that is running at 7.5 lines/sec because the voice coil scanner's objective lens can have a much higher collection efficiency.

A control system to control a voice coil and translation table in the polymer array analysis system of the present invention is illustrated in Figure 7. The control system includes a computer 200, for example, a 400 MHz Pentium II PC, with a (servo) motion controller 201. The motion controller 201 installed in (or connected to) the computer 200 accepts digital commands from the computer and produces an analog output in the range of -10 V to +10 V. The motion controller may be, for example, the Galil Motion Control (Mountain View, CA) model DMC-1710, the Delta Tau Systems (Northridge, CA) model PMAC-Lite, or various other controllers from other companies such as Motion Engineering Inc., etc.

An amplifier 206 (e.g., a linear or pulse-width-modulated servoamplifier), for example a Galil MSA-12-80, accepts the analog signal from the motion controller 201 via an interconnection module 204, for example Galil ICM-1900, and outputs the appropriate current to the voice coil 201. The amplifier 202 is provided with power by power supply 205, for example Galil CPS-15-40. An encoder system with a readhead 208 provides

position feedback to the controller. Suitable encoder systems with readhead 208 are quadrature-output encoders with resolutions of 1 micron to 0.1 micron. The encoder system may be, for example, Renishaw RGH22Z readhead and RGS-S scale. Other suitable encoders are manufactured by Zeiss and other companies.

Some motion controllers (e.g., the Galil DMC-1710) can be programmed to produce TTL output pulses when certain positions are reached. For every scan line, the controller can produce a "line clock" pulse, which instructs the data acquisition board to begin acquiring a block of data, and a series of "pixel clock" pulses (for example, one pulse for every 1.5 micron change in position), each of which triggers one A/D conversion. These clock pulses can be used to prevent the jitter that might otherwise appear in the images. Using this procedure, it is possible to take data bi-directionally and have the odd and even lines of the image aligned within a fraction of a pixel.

Finally, the control system of Fig. 7 includes a translation table controller (indexer) 202, for example a JMAR indexer, connected to the computer 200 via an RS-232 cable. The translation table controller 202 is connected to the translation table 203, for example a JMAR Precision Systems 2-axis Slimline translation table. Thus, the same computer may be used to control the movement of the voice coil 207 linear slide and the translation table 203 for quick and coordinated scanning of the polymer array 9.

Data acquisition with the voice coil scanner is similar to data acquisition with the galvo scanner described in U.S. patent application No. 08/856,642. Photomultiplier output current is converted to voltage by an op-amp circuit, low-pass filtered by, for example, a 4-pole Bessel filter, and digitized by a 12-bit or 16-bit data acquisition board, for example a Computer Boards Inc. (Middleboro, MA) model CIO-DAS16/M1. Currently two versions of the data acquisition software exist. One version takes 9216 data points per scan line, one data point every 1.5 microns. The other takes 4096 data points per scan line, one data point every 3.5 microns. Data are taken at the rate of 30 scan lines per second. Data are taken bidirectionally, i.e. odd-numbered scan lines are taken while the voice-coil-driven axis is moving in the +X direction and even-numbered scan lines are taken while the voice-coil-driven axis is moving in the –X direction. With either version of the software, two or more data points are summed if coarser resolution is desired. Data are displayed on a computer screen as gray-scale images and are written to disk as 16-bit binary files.

As illustrated above, the voice coil can be applied to move the polymer array in a fixed objective lens system or to move a scan head having the objective lens. In either case, the scan speed including acceleration is improved and the confocal microscope lens system is simple, efficient, and inexpensive. Therefore, a high performance, high throughput scanner is provided by the voice coil scanner of the present invention.

All other things (e.g., pixel size, scan speed, laser power, etc.) being equal, a voice coil scanner of the present invention will provide about 8 times as many detected photons per feature as a galvo scanner. Therefore, the voice coil scanner of the present invention will prove very useful as feature sizes of polymer arrays are reduced.

The present invention provides improved systems and methods for detection of fluorescence images on a substrate. It is to be understood that the above description is intended to be illustrative and not restrictive. Many embodiments will be apparent to those skilled in the art upon reviewing the above description. Although the above described systems and methods has been described primarily herein with regard to the detection of fluorescent marked targets, it will readily find application to other areas. For example, the detection apparatus disclosed herein could be used in the fields of catalysis, DNA or protein gel scanning, and the like. The scope of the invention should therefore be determined not only with reference to the above description but should also be determined with reference to the appended claims along with a full scope of equivalents to which the claims are entitled.

All publications, patents, and patent applications cited herein are hereby incorporated by reference in their entirety for all purposes.

WHAT IS CLAIMED IS:

1. A scanning system comprising:

a translation stage including a voice coil, a linear slide and a bracket connecting said voice coil to said linear slide, said bracket having a surface for mounting a polymer array.

2. The system of claim 1, wherein said scanning system further comprises a translation table having a surface and a guide portion of said linear slide is mounted to said surface of said translation table.

3. The system of claim 2, wherein a polymer array is mounted to said surface of said bracket and said polymer array is a packaged polymer array.

4. The system of claim 1, wherein said bracket is connected to said moving part of said linear slide at another surface of said bracket.

5. The system of claim 4, wherein said translation stage further comprises a scale on said bracket.

6. The system of claim 4, wherein said translation stage further comprises a reflector and an objective lens, instead of said polymer array, mounted to said surface of said bracket.

7. The system of claim 6, wherein said reflector is selected from the group consisting of a mirror and a turning prism.

8. The system of claim 5, further comprising a confocal microscope image detection device having an objective lens, and the system provides accurate and reliable image recognition using a pixel size of 3.5 μm or smaller.

9. The system of claim 8, wherein said objective lens is selected from the group consisting of a microscope objective lens, an aspheric lens with a doublet lens, an aspheric lens without a doublet lens, and a refractive/diffractive hybrid lens.

10. The system of claim 7, wherein said objective lens is selected from the group consisting of a microscope objective lens, an aspheric lens with a doublet lens, an aspheric lens without a doublet lens, and a refractive/diffractive hybrid lens.

11. The system of claim 5, further comprising a control system for controlling the motion of said translation stage.

12. The system of claim 11, wherein said control system includes an amplifier connected to said voice coil.

13. The system of claim 12, wherein said control system includes a motion controller and a computer for controlling scanning.

14. The system of claim 13, wherein said control system includes a readhead for sensing location of said translation stage.

15. The system of claim 14, wherein said control system includes an interconnection module connected to said readhead, said voice coil, and said motion controller

16. The system of claim 5, wherein said surface for mounting a polymer array is a planar surface and perpendicular to said another surface which is also a planar surface.

17. The system of claim 6, wherein said surface for mounting a polymer array is a planar surface and parallel to said another surface which is also a planar surface.

18. The system of claim 9, wherein said system scans a polymer array image size of 1 cm x 1 cm or larger.

19. A scanning system comprising:

a translation stage including a means for linear translation, and a means for connecting a voice coil to said means for linear translation, said means for connecting said voice coil to said means for linear translation includes a surface for securely mounting a polymer array.

20. The system of claim 19, wherein said means for linear translation is a crossed roller bearing linear slide that provides single axis translation and said

means for connecting said voice coil to said linear slide is a bracket made of a light weight rigid material.

21. A polymer array scanning system comprising:

a linear actuator having a permanent magnet portion and coil winding portion;

a linear slide; and

a bracket connecting said linear actuator to said linear slide, said bracket having a surface for mounting a polymer array.

22. The system of claim 21, wherein said linear actuator is a voice coil.

23. The system of claim 22, wherein said voice coil is selected from the group consisting of a slide type voice coil and a plunger type voice coil.

24. The system of claim 23, wherein said slide type of voice coil is a BEI Kimco LA14-24-000 voice coil and said plunger type voice coil is a BEI Kimco LA34-37-000A.

25. The system of claim 23, further including a scan head, instead of said polymer array, mounted to said second surface of said bracket, for scanning a laser light beam in a fast axis direction across a surface of a substrate.

26. The system of claim 25, wherein said scan head includes a reflector and an objective lens.

27. The system of claim 26, wherein said reflector is selected from the group consisting of a mirror and a turning prism.

28. A method of scanning comprising the steps of:

providing a translation stage having a linear slide, a voice coil, and a bracket, said bracket connecting said linear slide to said voice coil and for mounting a polymer array thereon; and

increasing scanning acceleration and scan line speed using a voice coil.

29. The method of claim 28, further comprising the step of providing the increased scanning acceleration movement to a polymer array.

30. The method of claim 29, further comprising the step of providing increased scanning acceleration movement to a scan head, instead of said polymer array, mounted to said bracket.

31. The method of claim 30, wherein said scan head includes a reflector and a lens selected from the group consisting of a microscope objective lens, an aspheric lens with a doublet lens, an aspheric lens without a doublet lens, and a refractive/diffractive hybrid lens.

32. A confocal microscope image detection system comprising:

a light source;

an optical train for directing light from said light source to a substrate and separating reflected light from said substrate from an emitted light from said substrate;

a focusing system for focusing the light from said light source on said substrate;

a detector for detecting said emitted light from said substrate;

a translation table for translating said substrate in a slow axis direction and a focus axis direction; and

a translation stage including a bracket having at least two mounting surfaces, said translation stage for scanning in the fast axis direction using a linear actuator with acceleration greater than that of a stepper motor so that time needed for scanning a scan line in the fast axis direction is reduced and thereby the amount of time to scan a predetermined array size is reduced.

33. The system of claim 32, wherein said translation stage is mounted to a surface of said translation table

34. The system of claim 33, wherein said linear actuator is a voice coil and a polymer array is fastened to at least one of said mounting surfaces.

35. A scanning system comprising means for moving a linear translation stage with a speed of at least 10 lines per second over a distance of at least 2 mm wherein said scanning system scans with a pixel size of 3.5 microns or less.

36. The scanning system of claim 35 wherein said speed is at least 20 lines per second.

37. The scanning system of claim 35 wherein said speed is at least 30 lines per second.

38. The scanning system of claim 37 wherein said pixel size is 2 microns or less.

39. The scanning system of claim 37 wherein said pixel size is 1.5 microns or less.

40. The scanning system of claim 35, 36, 37 or 38 wherein said distance is at least 5 mm.

41. The scanning system of claim 35, 36, 37 or 38 wherein said distance is at least 14 mm.

42. The scanning system of claim 35 wherein said means is a voice coil driven translation stage.

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